REMARKS

Claims 1-25 are in this application, with claims 9-25 currently pending for prosecution on the merits.

Claims 9, 10, and 14 have been amended to overcome the rejections under 35 USC 112, first and second paragraphs and to correct clerical and typographical errors without narrowing the scope of these claims. Support for replacement of "LPS" with "lipopolysaccharide" can be found in 4 of the specification. Support for the feature of "systemic lipopolysaccharide exposure" or "systemic exposure of lipopolysaccharide" in the amended claims can be found in the specification of U.S. Patent Application No. 09/535,390 at pp. 2-4, 6, and 9, Publication 20040101488 (hereinafter "Published Spec") at ¶¶2-4, 9, 19, and 37 (In this document, references to page numbers of the Specification correspond to the page numbers of the specification as filed, while paragraph numbers correspond to the numbered paragraphs in the Published Spec available on the U.S.P.T.O. website). Support for the features of "pathophysiological reactions" and "manifestations of septic shock" in amended claim 10 can be found at pp. 2, 8, 9, 11 and 13 (Published Spec, ¶¶4, 27, 37, 45, and 50.) The step of optionally administering additional treatment in claim 10 is supported by the specified time intervals of the invention, namely that multiple doses of curcumin are administered over time including after LPS exposure, as described in the Specification, pp. 5, 8-11 and 13 (See Published Spec, ¶¶16, 30, 31, 32, 38, 39, 41, 45, 50, and Table 1).

Claims 18-25 are added. Claims 18 and 19 are based upon previous claim 9. Support for the feature of "preventing lethality" in claim 18 can be found in the Specification, pp. 5, 7, 9-10, 13 and 15 (See Published Spec, ¶¶10, 12, 16, 21, 23, 36, 38, 39, 50, 53, and Table 1). The issue of enablement of this feature as raised by the Examiner's rejection of previous claim 9 is discussed below. Support for the feature of "reducing severity of symptoms" in claim 19 can be found in the Specification, pp. 1, 6-7, 9 and 13 (See Published Spec, ¶¶1, 21, 23, 37, and 50). The Examiner has acknowledged the sufficiency of the written description with regard to this feature as claimed in previous claim 9 on pages 4-5 of the Official Action.

Support for the specified time intervals occurring before, during or after systemic LPS exposure in claim 20 can be found in the Specification, pp. 5, 8-11 and 13 (See Published Spec, ¶¶16, 30, 31, 32, 38, 39, 41, 45, 50, and Table 1). Support for the specified time intervals occurring before, during and after systemic LPS exposure in claim 21 can be found in the Specification, pp. 5, 9-11 and 13 (See Published Spec, ¶¶16, 38, 41, 45, 50, and Table 1). Support for the markush group of pathophysiological reactions to LPS exposure in claim 22 can be found in the Specification, pp. 1 and 11, ¶¶4 and 45. The step of optionally administering additional treatment in claim 23 is supported by the specified time intervals of the invention as described in the Specification, pp. 5, 8-11 and 13 (See Published Spec, ¶¶16, 30, 31, 32, 38, 39, 41, 45, 50, and Table 1). Claim 24 is based in part upon previous claim 9. Support for the reduction of neutrophil infiltration in claims 24 and 25 can be found in the Specification, pp. 1-3, 5-7, 10 and 15 (See Published Spec, ¶¶1, 5, 11, 12, 13, 20, 22, 23, 24, 42, 51, 52, and 53).

The Examiner rejected previous claim 9 under 35 U.S.C. 112, first paragraph as not enabling for "preventing lethality" because of the absence of effective treatments of septic shock. Though the feature has been deleted from claim 9 as amended, Applicant respectfully traverses the rejection with respect to the feature as included in new claim 18.

The Examiner contends that the description does not provide the basis or the type of subject to which curcumin can be administered to prevent septic shock lethality, which he defines to require a complete cure or eradication effect. He argues that the specification does not demonstrate a correlation between the experiments conducted and the preventive utility claimed, stating that it would require painstaking experimental study for one skilled in the art to predictably determine in which subjects septic shock lethality would be prevented.

Applicant has described at least one embodiment of the claimed invention in the working examples, particularly example 7, in which mice were treated with varying doses of curcumin four and two hours prior to injection with LPS and survival was measured (See Specification, pp. 13-14, Published Spec, ¶50). New claim 18 is directed towards preventing lethality in an animal by treatment with curcumin. Measurement of survival after prophylactic

treatment in vivo clearly and directly correlates with the efficacy of such prophylaxis in preventing lethality. The Examiner has not alleged that an *in vivo* animal model is insufficient, and has not met his initial burden by providing reasons for a conclusion of a lack of correlation for an in vitro or in vivo animal model example (See MPEP 2164.02). Nonetheless, no undue experimentation would be necessary to enable a skilled artisan to carry out this embodiment of the claimed invention. See *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989) (description was enabling when only one embodiment and the method to determine its dose/response were set forth in the specification).

Further addressing the specific allegations of the Examiner, new claim 18 purports to prevent lethality, not to prevent the exposure or the disease. According to the Merriam-Webster Medical Dictionary Online (http://medical.merriam-webster.com/medical/lethality), the term "lethality" is the noun form of the term "lethal", meaning "of, relating to, or causing death" or "capable of causing death." If the Examiner's dictionary definition of "prevent" is accurate, than the phrase "preventing lethality" means "to anticipate or counter in advance the capability of septic shock to cause death."

The specification clearly describes a mechanism by which curcumin prevents LPS induced septic shock from causing death (see Specification, pp 3 and 14-15, Published Spec, ¶¶6 and 51 describing the mechanism of injury to the liver as the primary cause of septic shock-related death and Specification page 10, Published Spec ¶42, describing the effect of curcumin on neutrophil infiltration into the liver). It further provides examples including experiments in which curcumin served as a prophylaxis against septic death in 70% of mice (see Specification, pp. 5-6 and 14-15, Published Spec, ¶¶16 and 51-52 and Figure 1).

The invention of new claim 18 enables "preventing lethality" because the described regimen of administration of curcumin resulted in 70% survival of lipopolysaccharide (LPS) -challenged mice. Prevention need not be a complete cure or eradication, but rather, it must "anticipate or counter in advance the capability of septic shock to cause death". There is no

requirement that prevention must be 100% effective. Applicant respectfully submits that treatment of subjects suffering from LPS-induced septic shock by the method of new claim 18 prevents lethality in that it anticipates or counters in advance the mortality rate in the subject population. The method is thus a preventive measure taken to reduce the likelihood of death.

Therefore, it is respectfully submitted that the rejection be withdrawn.

Claim 9 stands rejected under 35 USC 102(b) as being anticipated by Aggarwal (WO/97/09877). Applicant respectfully traverses the rejection.

Claim 9 as amended is not anticipated by Aggarwal because Aggarwal does not disclose the feature of "systemic LPS exposure in an animal". Aggarwal describes that curcumin inhibits Tumor Necrosis Factor (TNF) - induced activation of Nuclear Factor - kappa B (NF-kB), and that the inappropriate regulation of NF-kB has been associated with septic shock as well as a number of other diseases, including cancers. Aggarwal acknowledged that many agents induce NF-kB activation (See Aggarwal, Page 1), but only studied curcumin's effect on TNF-induced NF-kB activation.

Further, Aggarwal only studied curcumin's effect on myelomonoblastic leukemia cells (See Aggarwal, Example 2, Page 7, Lines 20-22). Cancer cells, including those involved in leukemia, are known to have varied abnormal regulation of NF-kB (see Inoue et al, "NF-kB activation in development and progression of cancer", Cancer Sci, Vol. 98, No. 3, pp. 268-274 at 270 See attached; Grandage et al., "PI3-kinase/Akt is constitutively active in primary acute myeloid leukaemia cells and regulates survival and chemoresistance via NF-kB, MAPkinase and p53 pathways", Leukemia 19, pp. 586-593 at 591). Thus, Aggarwal studied curcumin's effect on TNF-induced NF-kB activation in cells that regulate NF-kB in a manner that does not correlate with such regulation in normal cells subjected to LPS exposure. Aggarwal therefore does not disclose curcumin's effect on normal cells subjected to LPS exposure.

Also, as described in the present application (See Specification, page 2, Published Spec, ¶4), LPS activates various cells, which release various mediators aside from TNF-α, namely IL-1, IL-6, IL-8, nitrous oxide, superoxide anions, and lipid mediators. Aggarwal

further did not disclose curcumin's effect on the NF-kB activation by the non-TNF mediators released in the presence of LPS. Aggarwal merely inferred without experimental basis that curcumin's effect on TNF-induced NF-kB activation may alleviate septic shock conditions. The simple statement that NF-kB may play a role in a laundry list of varied diseases was not sufficient disclosure that curcumin would inhibit NF-kB activation sufficiently to treat those diseases. Aggarwal does not provide a skilled artisan with any reasonable expectation of success in using curcumin to treat the different causes and conditions associated with each of the diseases, specifically LPS-induced septic shock. Given the laundry list of diseases recited and the limited disclosure of *in vitro* studies of NF-kB in individual cells, no conclusion that curcumin would treat the listed diseases with any reasonable expectation of success could be based on Aggarwal.

Additionally, Aggarwal did not describe physiological responses to LPS other than intracellular inhibition of NF-kB activation in individual cells. As an in vitro study, Aggarwal's disclosure does not address the clinical manifestations, physiological reactions, conditions and symptoms of systemic LPS exposure to normal subjects *in vivo* or the extent to which they can be inhibited by curcumin. Aggarwal therefore does not anticipate amended claim 9 because it does not disclose the feature of "systemic LPS exposure in an animal."

The Examiner argues that the features of "controlling neutrophil infiltration," "preventing lethality," and "reducing severity of symptoms" which are not described in Aggarwal, are inherently present in prior claim 9 since the prior art method employs the same compound in the overlapping concentration to the same treatment population for the same ultimate purpose. All three of these features have been deleted from amended claim 9 without intent to narrow the scope of the claim. These elements would be covered by claim 9 as amended, and Applicant is thus not estopped from asserting these features in other claims, as was done here.

The features of "controlling neutrophil infiltration", "preventing lethality" and "reducing severity of symptoms" have been incorporated from prior claim 9 individually into

amended claim 14 and new claims 18, 19, 24 and 25. and are not inherently present from the disclosure of Aggarwal. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Additionally, the treatment population is not the same, since Aggarwal studied only leukemia cells *in vitro* and provided insufficient basis for generalizing his results to other disease states as discussed above. In contrast to the present invention, Aggarwal describes a method of administering curcumin to leukemia cells *in vitro* to inhibit intracellular activation of NF-kB. Though NF-kB may be involved in septic shock, there is no disclosure that it serves any direct or primary role in the clinical manifestations of LPS induced septic shock that are treated by the method of the claimed invention.

Applicant further notes that the contention that "preventing lethality" is inherent in Aggarwal is contradictory to the Examiner's allegation against the enablement of "preventing lethality" in prior claim 9. In arguing that prior claim 9 did not enable "preventing lethality", the Examiner relied upon a 2002 article about septic shock therapy (See Official Action, Page 3). He stated as the basis for his contention that "preventing lethality" was not enabled that "there are still currently no effective treatments for septic shock". If no effective treatment existed as of the filing date of the present application, Aggarwal could not have prevented the lethality of septic shock and therefore the claim element of "preventing lethality" could not have been inherently anticipated.

Therefore, it is respectfully submitted that the rejection be withdrawn.

Claims 9-17 are rejected under 35 USC 103(a) as being unpatentable over Aggarwal in view of Ammon et al. (US 5401777) in further view of Nerenberg et al. (USP 6498147) and Hawiger et al. (USP 6495518). Applicant respectfully traverses the rejection.

The claimed invention is based at least in part upon Applicant's discovery that administration of curcumin to an animal exposed systemically to LPS reduces the symptoms of septic shock and prevents the likelihood that the systemic LPS exposure will cause death.

Aggarwal teaches the effect of pre-treatment with curcumin on activation of NF-kB, without disclosing: (1) the effects of curcumin on physiologic reactions to and resulting symptoms of LPS-induced septic shock, such as the infiltration of neutrophils to the tissues; (2) the effective use of curcumin not merely as a pretreatment, but also during and after exposure to LPS; and (3) the proper dosage and dose form of curcumin for treatment of LPS-induced septic shock conditions. There can be no reasonable basis with rational underpinning to support modification of Aggarwal based on the other references supplied by the Examiner to include the missing claim elements.

As discussed above, Aggarwal focuses solely upon curcumin's role with regard to TNF-induced activation of NF-kB in vitro, and fails to disclose the effects of curcumin on the symptoms of LPS-induced septic shock in vivo. Nerenberg and Hawiger, neither of which utilize curcumin, similarly only address intracellular regulation of NF-kB, and Ammon does not address LPS-induced septic shock conditions. The combined references therefore do not address the effects of curcumin on septic shock conditions, including the reduction or control of neutrophilic infiltration from blood vessels to underlying tissues as recited in amended claims 10 and 14 and the claims dependent thereon.

Applicant additionally notes that the step in claim 10 of "probing reduction in neutrophil infiltration from blood vessels to underlying tissues by staining and microscopically examining the extent of inflammation" is critical because neutrophil infiltration is the primary cause of symptoms and in the case of the liver tissue, death (See Specification, page 3, Published Spec ¶5). Since none of the references disclose the analysis of neutrophil infiltration, claim 10 and the claims dependent thereon are non-obvious.

Also, Aggarwal does not disclose effective treatment with curcumin during or after exposure to LPS, as is claimed in the present application in new claims 20 and 21. Rather, Aggarwal requires pre-treatment, having only found inhibition of TNF response when cells were treated with curcumin prior to TNF exposure (See Aggarwal, Example 7, Page 10, Lines 20-32 and Fig. 1b). If curcumin treatment was given simultaneously or subsequent to TNF

exposure, there was no inhibition of NF-kB (See Aggarwal, Fig. 1c). Neither Ammon, nor Nerenberg, nor Hawiger disclose that curcumin is effective in reducing LPS-induced septic shock conditions when administered after exposure. Ammon does not address LPS-induced septic shock conditions. Nerenberg describes pretreatment (See Nerenberg, Co. 12, Lines 59-60) with antisense oligonucleotides which bind to NF-kB mRNA to inhibit translation (See Nerenberg, Col. 3, Lines 54-60), and thus does not suggest post-exposure curcumin treatment. Though Hawiger describes treatment after exposure to LPS, he does not use curcumin, but rather a nuclear localization sequence of NF-kB to inhibit nuclear importation. Therefore, none of the references suggest concurrent or post-exposure treatment with curcumin. In fact, Aggarwal's requirement of pre-treatment teaches away from this feature. In contrast, the present invention found curcumin could inhibit LPS induced lethality not only when it was administered before exposure to LPS, but also when even when it was administered simultaneously or after LPS exposure (See Specification, Page 14, Published Spec ¶50, and Figs. 1-5).

As acknowledged by the Examiner (See Office Action, Page 9), Aggarwal does not teach the oral administration of the claimed invention. The Examiner contends that Ammon et al. disclose the "oral dose" form. However, Ammon et al. apply the oral dose for treatment of leucotriens and prostaglandins, and not to LPS induced septic shock. The dose form for one ailment cannot be extrapolated to other ailments.

Furthermore, Aggarwal does not teach the pharmacologically effective dosage of curcumin. Aggarwal teaches that the effective dose of curcumin is any dose which suitably inhibits the activation of NF-kB transcription factor, preferably 1-100 mg/kg. Aggarwal's claimed dosage is indefinite and lacks basis. The reference describes in vitro administration of curcumin to leukemia cells, and does not provide pharmacologic information with regard to gastroesophageal absorption to make any determination as to the appropriate amount of curcumin for oral administration to an animal.

The unfounded amount recited by Aggarwal makes no reference to the mode of

administration and provides no further description of the units of mg/kg. Kilograms of what? The recited varied concentrations up to 60 μM in the examples do not further clarify the meaning of the 1-100 mg/kg dosage units. Even if the suggested dosage was calculated based on the molecular mass of curcumin and the molar concentrations employed, it does not purport to take into account in vivo applications of the invention including the pharmacokinetics of oral absorption, the potential differences in curcumin's effects between myeloblastic leukemia cells and healthy leukocytes, or the clinical effect on neutrophilic infiltration. It is possible that the alleged pharmacologically effective amount recited in the reference would not therefore include or otherwise be comparable to that of the claimed invention. Furthermore, Aggarwal does not disclose any relationship between the proposed dosages and their effect on reducing or controlling of neutrophilic infiltration from blood vessels to underlying tissues or septic shock symptoms.

Even if Ammon supplies the oral dose form of curcumin, it teaches away from the high range of Aggarwal because it describes damage to the stomach mucosa at daily oral dosages of 100 mg/kg (See Aggarwal, Col. 5, Lines 14-20). Ammon further teaches away from the 40-60 mg/kg preferable pharmacologically effective dosage of amended claims 11 and 15 because it suggests dosages of 15-30 mg (See Aggarwal, Examples 1-5). While Nerenberg and Hawiger et al. discuss inhibition of NF-kB transcription factor for controlling septic shock, these references do not disclose the use of curcumin.

Therefore, it is respectfully submitted that the rejection be withdrawn.

Claim 17 is rejected under 35 USC 103(a) as being unpatentable over Aggarwal (WO/97/09877) in view of Schneider et al. (US 6013273) in further view of Nerenberg et al. (USP 6498147) and Hawiger et al. (USP 6495518). Applicant respectfully traverses the rejection.

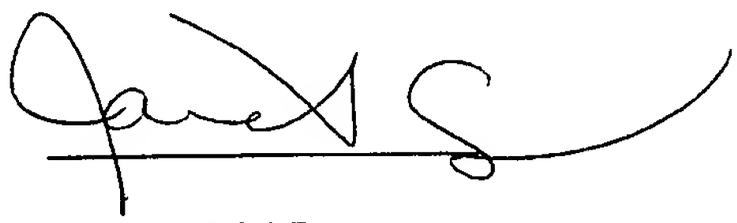
Schneider discloses use of choline in treating septic shock. In a preferable form, Schneider's invention includes omega-3 polyunsaturated fatty acids (PUFAs). It utilizes antioxidants to protect the PUFAs from peroxidation (See Schneider, Col. 4, Lines 37-44).

Schneider does not disclose the use of antioxidants for treatment of LPS-induced septic shock. It employs choline for such treatment, and merely uses antioxidants as a preservative for the PUFAs. Thus, Schneider provides no motivation to add antioxidants to curcumin. Accordingly, the Examiner has not stated a reasonable basis with rational underpinning to combine Schneider with Aggarwal, Nerenberg, and Hawiger such that treatment of LPS-induced septic shock with curcumin and antioxidants would be obvious.

Therefore, it is respectfully submitted that the rejection be withdrawn.

Applicants respectfully submit that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,



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